Remarks

Claims 1-10, 12-21, 23, 25-27 and 29-52 are pending in this application. Claim 38 is canceled herein without prejudice; thus, claims 11, 22, 24, 28, and 38 are canceled. Claims 39-52 are withdrawn from consideration.

Applicants acknowledge the Examiner's withdrawal of numerous rejections. Applicants, however, do not agree with the Examiner's justification for withdrawal of the 102(b) rejection based on Eng (U.S. Pat. No. 5,424,286). The Office Action states that a "converted population of cells inherently exists in the treated animals" based on the administration of GLP-1 and exendin-4 as insulinotropic agents. Such cells are not inherently taught by Eng or the remaining references cited under 102 for the reasons explained below.

Claims 1, 12, 23, 27, 31-34, 36 are amended herein to more particularly define the invention. Support for these amendments can be found in the original claim language and throughout the specification, as set forth below. It is believed that these amendments add no new matter. In light of these amendments and the following remarks, applicants respectfully request entry of these amendments, reconsideration of this application, and allowance of the claims.

35 U.S.C. § 112, first paragraph

A. Claims 2, 13, 25, 29, 34 and 35 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner states that with respect to claims 2, 13, 25, 29, the amended claims 1, 12, 23 and 27, from which claims 2, 13, 25 and 29 depend, recite the new limitation of "for at least twenty-four hours;" however, the specification indicates that the *in vitro* contacting of cells with GLP-1 is 3 days (Example 5, page 58, lines 7-8). The Examiner alleges that the scope of at least twenty-four hours and 3 days is different and that the amendment has changed the scope of the invention and is not supported by the original disclosure.

In the specification, on page 20, lines 10-28, applicants teach that the contacting of non-insulin producing cells with the growth factors is "for at least twenty-four hours." Thus, this limitation in the claims is not new matter; thus, there is no basis for this rejection. Applicants, therefore, respectfully request withdrawal of this rejection.

B. Claim 34 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter. Specifically, the Examiner states that the new limitation of "a subject *lacking insulin-producing cells*" is allegedly not supported by the instant specification. On page 2, lines 8-10, the specification states "In Type 1 diabetes, the beta cells are completely destroyed by the immune system, resulting in an absence of insulin producing cells." The specification further provides for treatment of a subject with Type 1 diabetes. Applicants respectfully point out that "[t]he subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement." M.P.E.P. § 2163.02 There is clear support in the specification for administering the growth factors of the invention to a subject lacking insulin-producing cells. Accordingly, Applicants request withdrawal of the rejection.

35 U.S.C. § 112, second paragraph

Claims 1-10, 12-21, 23, 25-27, 29, 30 and 32-38 remain rejected, and claim 31 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner states that the term "amino acid sequences substantially homologous" does not define the upper limit as to how many amino acids may be altered.

It would be clear to a person of skill what "amino acid sequences substantially homologous to..." means. As defined on page 530 of Webster's II New College Dictionary (attached as Exhibit A), "homologous" is defined as 1) "similar or corresponding in position, value, structure, or function" and 2) "corresponding in structure and evolutionary origin." When used in this context, the phrase "amino acid sequences substantially homologous to..." describes amino acid sequences that are "similar or corresponding in position, value, structure, or function"

and "corresponding in structure and evolutionary origin to a reference amino acid, e.g., GLP-1 and/or Exendin-4. One of skill in the art would recognize that the claims recite growth factors having amino acid sequences that correspond in position, value, structure and function as the referents, GLP-1 and Exendin-4. Therefore, it is not necessary to state an upper limit to the length of the claimed amino acid sequences because the claimed invention only includes those amino acid sequences (growth factors) that correspond in structure and function to the referents, GLP-1 and Exendin-4. Thus, applicants believe the metes and bounds of the claim can be determined by one of skill, and, thus, there is no basis for this rejection. In an effort to facilitate prosecution, however, Applicants herein amend claims 1, 12, 23, 27, 31-34, and 36 to recite that the growth factors and fragments thereof having amino acid sequences substantially homologous to GLP-1 or Exendin-4 comprise five essential amino acid residues and have the differentiating function. These claim amendments are supported by the specification on page 17, line 25, through page 18, line 2, and no new matter is believed to be added by the amendments. Therefore, applicants respectfully request reconsideration and withdrawal of this rejection.

35 U.S.C. § 112, first paragraph

A. Claims 1-10, 12-21, 23, 25-27 and 29, 30-38 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for claims limited in scope to an isolated population of insulin-producing cells made by contacting GLP-1 or exendin-4, allegedly does not reasonably provide enablement for claims to an isolated population of insulin-producing cells made by contacting growth factors having amino acid sequences substantially homologous to GLP-1 or exendin-4, or fragment thereof. The Examiner states that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

If the examiner believes that there is a scope issue with enablement rather than an issue of any enablement, the examiner should point out limitations that the examiner believes would render the claims enabled (MPEP 2164.04, 2164.08), in addition to evidence supporting that conclusion. The Examiner has failed to carry this burden.

The Examiner goes on to state that the claim limitation of "growth factors having amino acid sequences substantially homologous to GLP-1 (or exendin-4)" in claims 1, 12, 23, 27, 31-34, and 36, given the broadest interpretation, reads on any or all possible functional equivalents of GLP-1 or exendin-4 based on the definition in the specification, which defines such as polypeptides that include one or more additions, deletions or substitutions in the amino acid sequence without appreciable loss of functional activity as compared to GLP-1 or exendin-4 in terms of the ability to differentiate insulin-producing cells from non- insulin-producing cells (the paragraph bridging pages 15-16), and does not give upper limit as to the number of amino acid changes. The Examiner alleges that any functionally equivalent protein with no structure similarity to GLP-1 or exendin-4 would meet the limitation.

With regard to the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *In re Moore*, 439 F.2d 1232, 1236, (CCPA 1971). The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the Examiner determine exactly what subject matter is encompassed by the claims. The Examiner should determine what each claim recites and what the subject matter is when the claim is considered as a whole, not when its parts are analyzed individually. The determination of the propriety of a rejection based on the scope of a claim relative to the scope of the enablement involves two stages of inquiry. The first is to determine how broad the claim is with respect to the disclosure. The entire claim must be considered. The second inquiry is to determine if one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation. M.P.E.P. § 2164.08.

The Examiner has not carried the burden of determining the proper scope of the claims relative to the scope of the enablement disclosed in the specification. In the first step of the inquiry, the Examiner has failed to examine the claims as a whole. By focusing on the clause "growth factors having amino acid sequences substantially homologous to GLP-1 and/or

Exendin-4," the Examiner fails to put the clause into proper context. Specifically, the Examiner's allegation that "[t]he claim limitation of 'growth factors having amino acid sequences substantially homologous to GLP-1 (or exendin-4)' in claims 1, 12, 23, 27, 31-34, and 36, given the broadest interpretation, reads on any or all possible functional equivalents of GLP-1 or exendin-4 based on the definition in the specification.... As such, any functionally equivalent protein with no structure similarity to GLP-1 or exendin-4 would meet the limitation" is wrong.

The Examiner incorrectly defines the term "homologous" to mean only "having the same function." However, as noted above, the term homologous means "similar or corresponding in position, value, structure, or function" and 2) "corresponding in structure and evolutionary origin." Thus, the phrase "amino acid sequences substantially homologous to..." describes amino acid sequences that are "similar or corresponding in position, value, structure, or function" and "corresponding in structure and evolutionary origin" to a reference amino acid sequence, e.g., GLP-1 and/or Exendin-4. One of skill in the art would, therefore, recognize that the claims recite growth factors having amino acid sequences that substantially correspond to the structure and function of the referents, GLP-1 and Exendin-4, and not just to function alone. Because the Examiner has ignored the "structure" element of the definition of "homologous," the scope of the claims has been incorrectly determined. Because the result of the first step of the inquiry is wrong, the second step of the inquiry cannot be made correctly.

Based on an erroneous interpretation of the scope of the claims, the Examiner alleges that

> [e]nablement is not commensurate in scope with claims to any or all possible functional equivalents of GLP-1 or exendin-4. It is noted that the patentability of the claimed 'growth factors' rests not on the biological property, but rather the particular sequences disclosed in the specification as filed because there exist other distinct proteins with the same or similar biological properties. Since there is no upper limit given as to the number of amino acid changes, any functionally equivalent polypeptide with no structure similarity to GLP-1 or exendin-4 would meet the limitation. Additionally, the specification provides no information about the relationship of the function and structure of GLP-1 and exendin-4, nor enough

> guidance to teach how to make a commensurate number of the claimed species without altering the biological property. Therefore, it is not predictable what essential structures are required for the protein to be functional, and it would require undue experimentation to determine such.

See Office Action, page 6, paragraph 1 (emphasis added).

The Examiner goes on to state that the factors considered when determining whether the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Given the state of the art, two amino acid sequences and identification of essential residues, one of skill would know how to make and use growth factors that are substantially homologous to the known polypeptides GLP-1 and/or Exendin-4. Applicants teach that the claimed homologous growth factors can be made with additions, deletions, and substitutions of amino acids in the amino acid sequences of GLP-1 and/Exendin-4 that do not significantly change their structure and ability to differentiate insulin-producing cells from non-insulin-producing cells. See in the specification page 15, line 18 to page 16, line 2. These methods are well known in the art. Moreover, it would be routine for one of skill to make the homologous growth factors and test them for their function.

The claims recite a growth factor selected from the group consisting of GLP-1 and/or Exendin-4, growth factors having amino acid sequences substantially homologous to GLP-1 and/or Exendin-4, and fragments thereof. Moreover, on page 15, line 30 to page 16, line 14, applicants teach that the substantially homologous polypeptides are made by conservative modifications and changes in the amino acid sequence of GLP-1 and/or Exendin-4, the resulting protein having like characteristics. Furthermore the specification, page 17, line 22 to page 18,

line 2, points to references teaching fragments and homologous sequences and specifically teaches five highly conserved amino acid residues that should be conserved in the modified sequences. Thus, the Examiner errs when stating "the specification provides no information about the relationship of the function and structure of GLP-1 and exendin-4." One of skill in the art would recognize that "substantially homologous" requires similar structure and function and would recognize the specific amino acids that must be conserved to maintain the desired function.

The Examiner notes that the description of claimed proteins via a biological function is similar to the situation in *Ex parte Maizel* (27 USPQ2d 1662 at 1665) in which it was found that

> Appellants have not chosen to claim the DNA by what it is but, rather, by what is does, i.e., encoding either a protein exhibiting certain characteristics, or a biologically functional equivalent thereof. Appellants' claims might be analogized to a single means claim of the type disparaged by the Court of Customs and Patent Appeals In re Hyatt, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983). The problem with the phrase "biologically functional equivalent thereof" is that it covers any conceivable means, i.e., cell or DNA, which achieves the stated biological result while the specification discloses, at most, only a specific DNA segment known to the inventor. Clearly the disclosure is not commensurate in scope with the claims.

The Examiner alleges that the instant claims do not positively identify the protein of the invention by its sequence, but rather define such in terms of its biological activity. Therefore, the currently pending claims are analogous to the DNA claims in Maizel, in which the DNA was defined by the biological activity of the protein it encoded.

As noted above, applicants rely upon the common usage of the term "homologous" and recite proteins that are similar in structure and biological activity, i.e., function. Unlike in *Maizel*, applicants teach proteins that are substantially homologous to GLP-1 and Exendin-4 whose respective structures are well known in the art. Thus, the claimed growth factors are not defined only by their biological activity, but they are also defined by the structural limits of the referent compounds, GLP-1 and Exendin-4. Applicants, in an effort to facilitate prosecution,

have amended claims 1, 12, 23, 27, 31-34, and 36 to specify that the growth factors and fragments thereof having amino acid sequences substantially homologous to GLP-1/Exendin-4 comprise five essential amino acid residues and have the differentiating function. As discussed above, these claim amendments are supported by the specification on page 17, line 25, through page 18, line 2, and no new matter is believed to be added by the amendments. Therefore, applicants believe that there is no basis for these rejections and respectfully request their withdrawal.

B. Claims 1, 12, 23, 27, 31-34, and 36 are further rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which allegedly was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner states that "the claims recite 'growth factors having amino acid sequences substantially homologous to GLP-J (or exendin-4), and fragment thereof;' however, the specification merely exemplifies a few growth factors capable of differentiating a non-insulin producing cell into a insulin producing cell, such as hepatocyte scatter factor and activin A, without specifying sequence similarity (page 15, lines 16-20), and there is no such growth factor meeting the limitations of the claim identified or particularly described in the specification." See page 7, paragraph 3 of the Action.

The Written Description Guidelines, effective as of January 5, 2001, state "[w]hether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." See 3(c)(ii).

The level of skill and knowledge in the art is high. Moreover, applicants provide detailed, known referent structures, i.e., the amino acid sequences of GLP-1 and Exendin-4. Applicants also teach that the function of these growth factors is the differentiation of non-insulin-producing cells into insulin-producing cells. By "substantially homologous" is meant by one skilled in the art to mean an amino acid sequence that includes conservative amino acid substitutions or high sequence identity. Further, applicants teach how to make the claimed substantially homologous growth factors. See in the specification, page 15, line 30 to page 16, line 14. Thus, substantial structure is indeed provided because the claims recite growth factors substantially homologous to GLP-1 and Exendin-4. Moreover, the recited growth factors have a common function, i.e., the differentiation of non-insulin-producing cells into insulin-producing cells. Thus, because structure and common function are described in the specification, one of skill in the art would recognize that applicants were in possession of the claimed growth factors at the time of filing of the application. Furthermore, claims 1, 12, 23, 27, 31-34, and 36 are amended to recite that the growth factors and fragments thereof having amino acid sequences substantially homologous to GLP-1/Exendin-4 comprise five essential amino acid residues and have the differentiating function. Applicants, therefore, respectfully request reconsideration and withdrawal of this rejection.

35 U.S.C. § 102

A. Claims 23, 26, 27, 30, 31 and 36-38 remain rejected, and claim 31 is rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Eng, U.S. Patent No. 5,424,286. The Examiner alleges that the claims are inherently anticipated by the '286 patent and states that *In re Zierden*, 162 USPQ 102 (CCPA 1969), does not apply to the method of converting non-insulin producing cells into insulin producing cells. Further, the Examiner states that the previous amendment of the claims by adding the limitation of "at least twenty-four hours" does not overcome the rejection because even though the '286 patent does not mention explicitly contacting the cells with GLP-1 for at least 24 hours, it is allegedly inherent as the method steps and the mean of administration are the same as that of the present invention. The Examiner also

alleges that the contacting in the prior art has to be at least 24 hours because there is no way to take the GLP-1 away once it is injected into a subject.

For a prior art reference to anticipate a claimed invention, each and every element of the claimed invention must be disclosed in that single reference. Further, the disclosure in that single reference must be enabling. If one element of the claimed invention is not disclosed in the prior art reference, there is no anticipation. It is settled law that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently." *Verdegaal v. Union Oil*, 814 F2d. 628, 2 U.S.P.Q.2d 1051 (Fed. Cir. 1987).

Claims 23, 27, 31 and 36 recite the limitation "for at least twenty-four hours." The '286 patent does not expressly disclose each and every element of these claims. Specifically, the '286 patent does not teach that the growth factor contacts non-insulin-producing cells for at least twenty-four hours. Furthermore, the patent does not teach that non-insulin-producing cells are differentiated into insulin-producing cells by contact with a growth factor for at least twenty-four hours. In fact, none of the experiments lasted longer than 4 hours. See Figure 3, '286 patent. Thus, because the '286 patent does not disclose each element of the claimed invention, i.e., "for at least twenty-four hours" and "differentiation," there is no anticipation.

Regarding inherency, M.P.E.P. § 2112 requires the Examiner to provide a rationale or evidence tending to show inherency. "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App.& Inter. 1990) (Emphasis in original). Thus, for a claim to be rejected on the basis of inherency, the Examiner has the burden to show that a missing element of a claim is inherently present in the prior art and that this missing descriptive matter would be recognized by persons of skill in the art.

The prior art does not inherently anticipate the claimed invention. Further, applicants

respectfully assert that the Examiner has incorrectly construed the case law previously argued. Specifically, the Examiner has misinterpreted *In re Zierden*, 162 USPQ 102 (CCPA 1969). In *In re Zierden*, the question presented was whether claims to a method of removing alluvium from industrial waters, for example, water in cooling systems, were anticipated by a prior art reference [French patent] that disclosed a method for treating industrial waters to remove calcium carbonate scale that builds up in such cooling systems. The court held that because the prior art reference did not inherently teach that the industrial waters contained alluvium, the disclosed method did not necessarily result in the removal of alluvium. Thus, there was no anticipation of the claimed invention.

The dissenting judge stated that "if the industrial waters of the [prior art] French patent contain alluvium, even in a very slight amount, then the process of that patent inherently anticipates appellant's process as claimed here." (Emphasis added). There was no dispute between the majority and the dissent that if alluvium had been present in the waters, the prior art process would have inherently removed the alluvium. Further, it was not disputed that it was very likely that alluvium was present in the waters. The majority opinion was based on the lack of certainty that alluvium was present in the waters.

The Examiner states "as the industrial waters may contain different ingredients, which may not be removed by the same method, teachings regarding the removal of one specific element may not inherently teach the removal of a different chemical entity." See paragraph bridging pages 8 and 9 of the Action. *In re Zierden*, however, is not about whether a method of removing one chemical entity from industrial waters would remove a different chemical entity from the same waters. Instead, this case held that a previously disclosed method of removing chemicals from industrial waters cannot anticipate a claim reciting a method of removing a particular chemical from industrial waters unless the particular chemical is known for certain to be present in the industrial waters.

In *Hansgirg v. Kemmer*, 102 F.2d 212, 40 USPQ 665 (CCPA 1939), the court emphasized that, for a prior art reference to anticipate a claimed invention, the matter not explicitly described in the reference must necessarily be present in the reference. The court held that "[i]nherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."

The law on probabilistic inherency is set forth in *Continental Can v. Monsanto*, 948 F.2d 1264, 20 USPQ2d 1746 (Fed. Cir. 1991). The court held that "[t]o serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." (Emphasis added).

With regard to the Office Action's rejection of claims 23, 26, 27, 30, 31 and 36-38 on the basis of inherency, the Office has the burden of showing that the '286 patent inherently describes an isolated population of insulin producing cells made by a process comprising contacting, for at least twenty-four hours, non-insulin producing cells with a growth factor selected from the group consisting of GLP-1 and/or exendin-4, growth factors having amino acid sequences substantially homologous to GLP-1 and/or exendin-4, and fragments thereof.

The '286 patent teaches pharmaceutical compositions containing exendin-4, fragments thereof, and methods for the treatment of diabetes mellitus. The patent further teaches "a method for the enhancement of insulin production or expression which comprises the steps of providing to a mammalian beta type pancreatic islet cell an effective amount of the insulinotropic peptides" disclosed. The patent does not mention differentiating non-insulin-producing cells into insulin-producing cells and does not teach contact for twenty-four hours. In *Hansgirg*, the issue was whether a prior art reference anticipated a method claim for obtaining purified magnesium. The court found that the prior art reference did not anticipate the claimed invention, noting "[n]othing is disclosed in his application that he sought to separate dust from vapor or that it was any part of

the problem he was attempting to solve." Similarly, nothing is disclosed in the '286 patent to demonstrate that differentiating non-insulin-producing cells into insulin-producing cells was part of the problem to be solved.

Further, the Office is incorrect when it alleges that methods of stimulating insulin release in a mammal as taught in the '286 patent "are the same" as the claimed methods and that the methods as taught in the '286 patent necessarily differentiate non-insulin-producing cells into insulin-producing cells. The '286 patent teaches contacting beta cells with exendin-4 for one hour (Example 4), and administering repeated boluses of exendin-4, as shown in Figure 3. In contrast, the instant application teaches an isolated population of insulin producing cells made by a process comprising contacting, for at least twenty-four hours, non-insulin-producing cells with a growth factor selected from the group consisting of GLP-1 and/or exendin-4, growth factors having amino acid sequences substantially homologous to GLP-1 and/or exendin-4, and fragments thereof. Applicants disclose that it took at least twenty-four hours for non-insulin-producing cells to differentiate into insulin-producing cells. See in the specification Example 3, page 41, lines 19-22. Thus, in the method of the '286 patent, in which contact between non-insulin-producing cells and exendin-4 lasted for only a few hours, a person of skill would not expect to find differentiation of those cells into insulin-producing cells, and, more significantly, the differentiation of the cells would not necessarily flow from the limited contact..

The Examiner also errs when she alleges that "the contacting in the prior art has to be at least 24 hours because there is no way to take the GLP-1 away once it is injected into a subject." The Examiner ignores the presence of degradative enzymes in the subject. The instant application states on page 18, line 25 to page 19, line 6 that

> [b]y "contacting " is meant an instance of exposure of the extracellular surface of a cell to a substance at physiologically effective levels. A cell can be contacted by a growth factor, for example, by adding the growth factor to the culture medium (by continuous infusion, by bolus delivery, or by changing the medium to a medium that contains growth factor) or by adding the growth factor to the intracellular fluid in vivo (by local delivery, systemic delivery, intravenous

> injection, bolus delivery, or continuous infusion). The duration of "contact" with a cell or group of cells is determined by the time the substance, in this case a growth factor, is present at physiologically effective levels in the medium or extracellular fluid bathing the cell. GLP-1 has a short half-life of several minutes, whereas Exendin-4's half-life is substantially longer, on the order of hours. A bolus of GLP-1 would, therefore, have contact with the cell for minutes, and a bolus of Exendin-4 would contact the cell for hours.

Thus, contact between GLP-1 and a cell lasts only a few minutes following a bolus injection, not because the GLP-1 is "taken away," but because it is rapidly degraded by dipeptidyl peptidase IV *in vivo*. The '286 patent teaches giving GLP-1 only over a short period of time. One of skill would know that the bioactivity of GLP-1 would be gone within minutes. In contrast, the instant application teaches that continuous infusion of GLP-1, whereby a physiologically effective level of GLP-1 is continuously maintained, results in an increase in the total number of insulin positive cells and in differentiation of acinar cells into insulin, IDX-I positive cells. The effect was observed as early as 1 day, and the maximal effect as early as seven days. See in the specification page 41, lines 5-15.

The Office has failed to meet its burden of showing that the missing matter in the '286 patent, i.e., an isolated population of insulin-producing cells made by a process comprising contacting, for at least twenty-four hours, non-insulin-producing cells with a growth factor selected from the group consisting of GLP-1 and/or exendin-4, growth factors having amino acid sequences substantially homologous to GLP-1 and/or exendin-4, and fragments thereof, is necessarily present. *Hansgirg*, 102 F.2d 212.

It is error for the Office to reject claims 23, 26, 27, 30, 31 and 36-38 just because it is possible or even probable that some of the insulin-producing cells claimed in the instant application may have been present in the '286 patent. The Examiner has failed to show with certainty that the missing matter (the cells) is present, and, thus, there can be no anticipation of

these claims based on inherency. Therefore, applicants respectfully request that this rejection be withdrawn and that amended claims 23, 27, 31 and 36 and dependent claims 26, 30, and 37-38 be allowed.

The Office alleges that the '286 patent anticipates claim 36 because the patent teaches an insulinotropic function of GLP-1 and Exendin-4. Applicants respectfully point out that the '286 patent teaches that the growth factors have an insulinotropic effect on the beta cells of a subject, and there is no suggestion that contact between non-insulin producing cells and the growth factors should continue for at least twenty-four hours days and that such contact would differentiate those cells into insulin-producing cells to induce insulin secretion. Applicants request reconsideration of the rejection.

B. Claims 23, 26, and 31 remain rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Dupre (WO 95/31214). Specifically, the Office Action alleges that although the prior art reference does not mention the mechanism of GLIP on differentiating non-insulin-producing cells into insulin-producing cells, a newly discovered mechanism does not make the product novel, nor change the outcome of a method with the same method steps. The Office Action goes on to allege that even though the prior art reference teaches a two-hour infusion of GLIP instead of teaching maintaining contact between non-insulin producing cells and GLIP for at least twenty-four hours, there is no way to stop contacting once the drug is administered under said circumstance, and thus if a bolus injection, for example, is sufficient to serve the purpose, a two hour infusion would be able to do the same. The Office continues to allege that a population of insulin-producing cells would inherently exist in the patients treated according to the method disclosed in the prior art because the steps are the same as the steps disclosed in the instant application.

As stated above, the Office errs when it alleges that the steps of the method taught in the prior art are the same steps of the method taught in the instant application. Also as noted above, the Office errs when it alleges that a two-hour infusion of GLIP will result in contact between

GLIP and non-insulin-producing cells for at least twenty-four hours because "there is no way to stop contacting once the drug is administered under said circumstance, and thus if a bolus injection, for example, is sufficient to serve the purpose, a two hour infusion would be able to do the same." See page 10, first full paragraph of the Action.

As taught throughout the application, contacting a non-insulin-producing cell for at least twenty-four hours with a recited growth factor is necessary for the non-insulin-producing cell to differentiate into an insulin-producing cell. Thus, the method of the prior art that teaches administering the growth factor for up to two hours does not teach contact for twenty-four hours; thus, the prior art does not expressly anticipate claims 23, 26, and 31. Also, as noted above, because the half-life of GLIP is very short (about two minutes), a two-hour infusion of GLIP cannot result in contact between non-insulin-producing cells and the growth factor for at least twenty-four hours. The Office's allegation that the GLIP, once administered, cannot be removed lacks scientific basis and is clearly unwarranted.

Claims 23 and 31 recite the phrase "for at least twenty-four hours." Claim 26 depends upon claim 23. WO 95/31214 does not expressly disclose each and every element of these amended claims. Specifically, the patent does not teach that the growth factor contacts non-insulin-producing cells for at least twenty-four hours. In WO 95/31214, the growth factor was administered to subjects for no greater than 2 hours. Therefore, claims 23, 26 and 31 cannot be rejected on the basis of express anticipation.

With regard to the Office's rejection of claims 23, 26 and 31 on the basis of inherency, the Office has the burden to show that WO 95/31214 inherently describes an isolated population of insulin producing cells made by a process comprising contacting, for at least twenty-four hours, non insulin-producing cells with a growth factor selected from the group consisting of GLP-1, growth factors having amino acid sequences substantially homologous to GLP-1, and fragments thereof.

WO 95/31214 teaches the use of GLIP in combination with insulin for treating Type 1 diabetes. The subjects diagnosed with Type 1 diabetes were in remission and were characterized "by substantial remaining endogenous insulin secretion." See page 5, lines 4-7. The patent also teaches that GLIP alone, when administered in a two hour infusion, can be used to treat Type 1 diabetic patients who have some endogenous insulin secretion because GLIP stimulates insulin secretion from pancreatic beta cells and helps to control the rise in blood sugar after a meal because it delays gastric emptying. Thus, this patent discloses that GLIP can be used to treat diabetics who can still secrete insulin based on two different mechanisms, i.e., by stimulating insulin secretion from insulin-producing cells and/or by delaying gastric emptying.

WO 95/31214 does not teach the use of GLIP for treating diabetic patients who no longer have endogenous insulin secretion and thus does not suggest the use of GLIP or other growth factors for differentiating non-insulin producing cells into insulin producing cells. Nothing is disclosed in WO 95/31214 to demonstrate that differentiating non-insulin-producing cells into insulin-producing cells was part of the problem to be solved.

Further, it is erroneous to assume that methods of stimulating insulin release in a mammal as taught in WO 95/31214 necessarily differentiates non-insulin-producing cells into insulin-producing cells. The patent teaches administering GLIP in a two hour infusion, alone or in combination with insulin, to stimulate endogenous secretion of insulin in patients with insulin-secreting cells. In fact, the patent discloses that "[i]t may be that the improved glycaemic control seen with GLIP administration in Type 1 diabetics is due to delay of the post-meal rise in blood glucose through the interval required for the establishment of the effect of insulin." See page 6, lines 14-18.

In contrast, the instant application teaches an isolated population of insulin-producing cells made by a process comprising contacting, for at least twenty-four hours, non-insulin-producing cells with a growth factor selected from the group consisting of GLP-1 and/or exendin-4, growth factors having amino acid sequences substantially homologous to GLP-1

and/or exendin-4, and fragments thereof. Applicants disclose that it took at least twenty-four hours for non-insulin-producing cells to differentiate into insulin-producing cells. See in the specification page 41, lines 19-22. Thus, in the method of WO 95/31214, in which contact between non-insulin-producing cells and GLIP lasted for only about two hours, a person of skill would not expect to find differentiation of those cells into insulin-producing cells.

The Office has the burden to show that the missing matter in this reference, an isolated population of insulin producing cells made by a process comprising contacting, for at least twenty-four hours, non insulin producing cells with a growth factor selected from the group consisting of GLP-1 and/or exendin-4, growth factors having amino acid sequences substantially homologous to GLP-1 and/or exendin-4, and fragments thereof, is necessarily present. *Hansgirg*, 102 F.2d 212. Even if the Examiner thinks it is possible or even probable that some of the insulin-producing cells claimed in the instant application may have been present in WO 95/31214, the legal standard is not satisfied. The Examiner has failed to show with certainty that the missing matter (the cells) is present, and, thus, there can be no anticipation of these claims based on inherency. Therefore, applicants respectfully request that this rejection be withdrawn and that claims 23 and 31 and dependent claim 26 be allowed.

C. Claim 31 remains rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Mashima et al. (Endocrinology, 1996, 137(9): 3969-76). The Examiner alleges that Mashima's hepatocyte growth factor (HGF) anticipates the claimed invention.

Claim 31 is amended herein by adding the phrase "excluding hepatocyte growth factor." Support can be found in the specification on page 15, lines 3-9. Applicants believe that this amendment overcomes the rejection and respectfully request its withdrawal.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application are believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

No fee is believed to be due; however, the Commissioner is hereby authorized to charge any fees which may be required or to credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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Michael Laird

10/7/03
Date